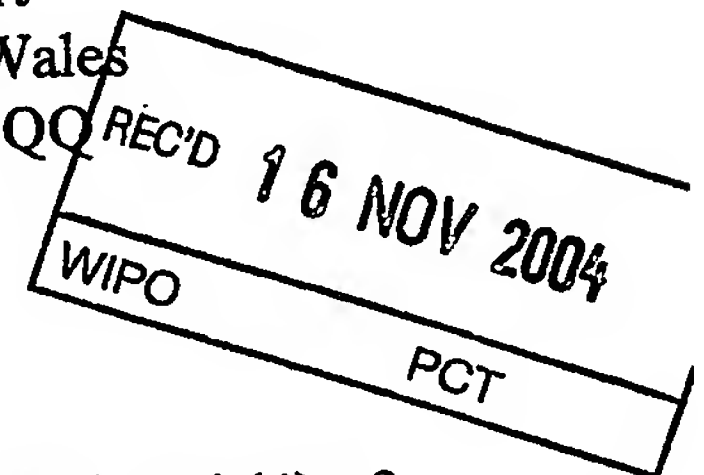




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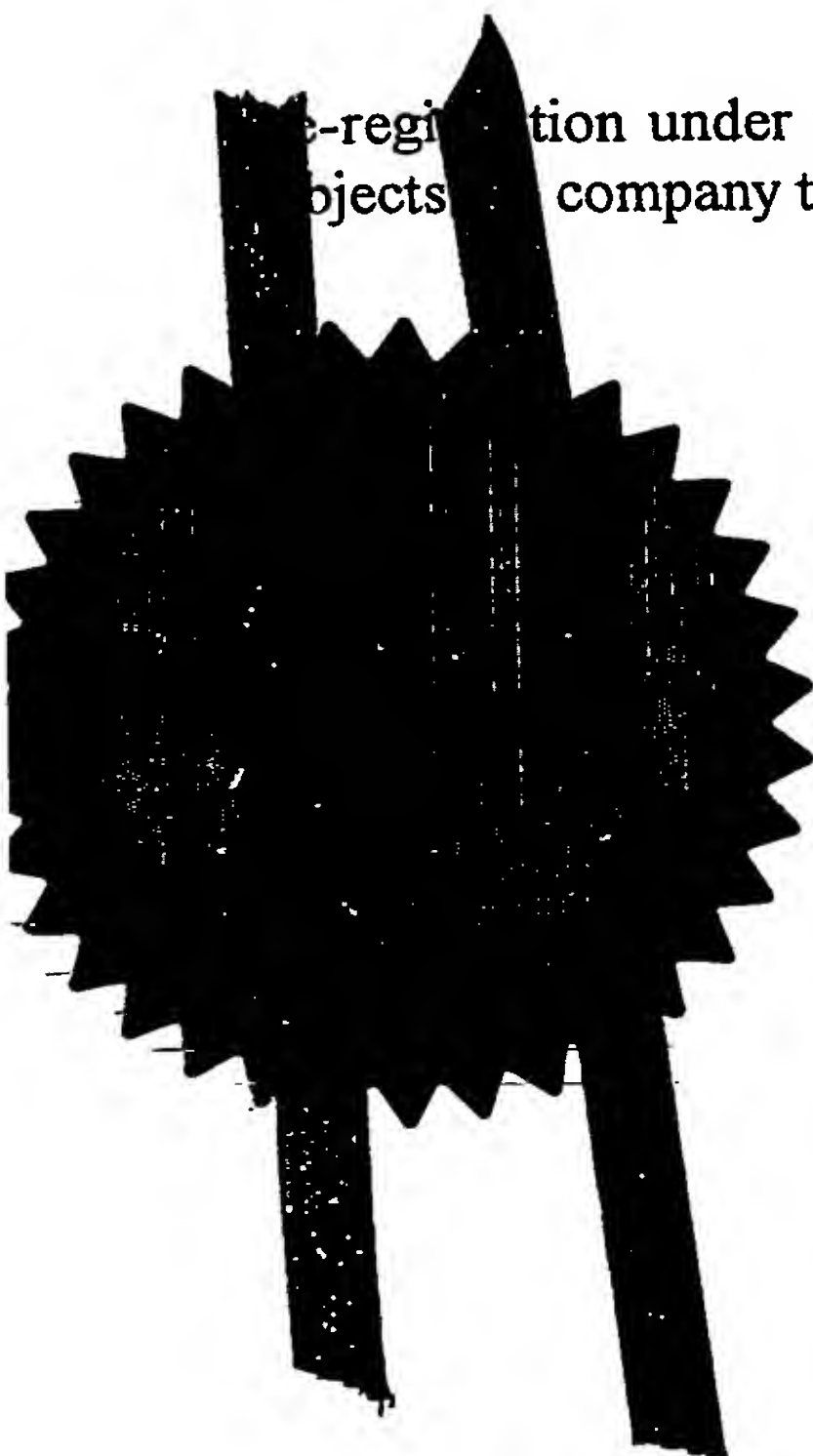
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Glaxo Group Limited
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Compounds

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COMPOUNDS

This invention relates to cyclohexene compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular
5 their use in the treatment of conditions mediated by the action of PGE₂ at EP₁ receptors.

The EP₁ receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE₂. PGE₂ also has affinity for the other EP receptors (types EP₂, EP₃ and EP₄). The
10 EP₁ receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP₁ receptor.

A number of review articles describe the characterization and therapeutic relevance of the
15 prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Macclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function*, S Narumiya et al, *Physiological Reviews* 1999, 79(4), 1193-126. An
20 article from *The British Journal of Pharmacology*, 1994, 112, 735-740 suggests that Prostaglandin E₂ (PGE₂) exerts allodynia through the EP₁ receptor subtype and hyperalgesia through EP₂ and EP₃ receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation*, 2001, 107 (3), 325 shows that in the EP₁ knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP₁ receptor antagonist (ONO-8711)
25 reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. S. Sarkar et al in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP₁ receptor antagonists in the treatment of visceral pain in a human model of
30 hypersensitivity. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based
35 side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDs and/or
40 COX-2 inhibitors.

In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE₂-induced hyperthermia in the rat is mediated predominantly through the EP₁ receptor.

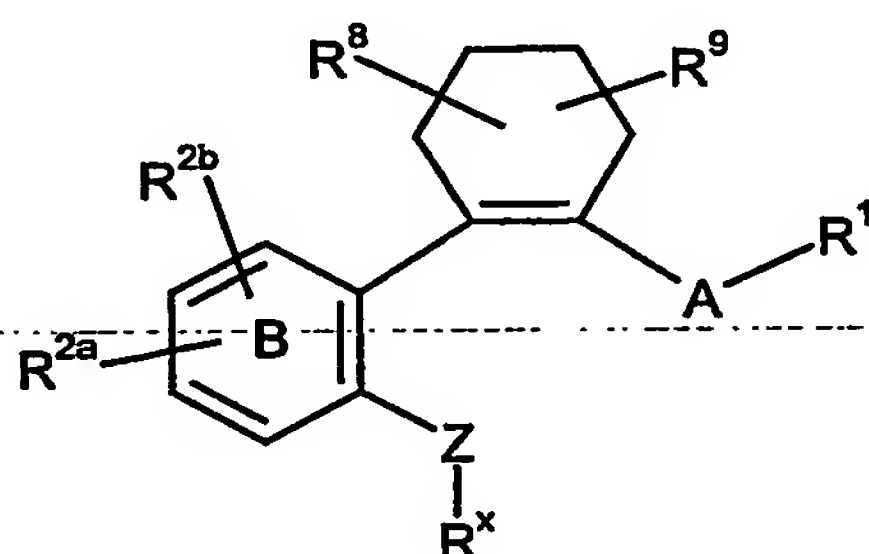
WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the

5 treatment of prostaglandin mediated diseases.

It is now suggested that a novel group of cyclohexene derivatives surprisingly are selective for the EP₁ receptor over the EP₃ receptor, and are therefore indicated to be useful in treating conditions mediated by the action of PGE₂ at EP₁ receptors. Such conditions

10 include pain, or inflammatory, immunological, bone, neurodegenerative or renal disorders.

Accordingly the present invention provides compounds of formula (I):



(I)

15

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

B represents a phenyl or pyridyl ring;

20 Z represents O, S, SO, or SO₂;

R¹ represents CO₂H, CN, CONR⁵R⁶, CH₂CO₂H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO₂alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

25 R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR⁴, O and SO_n,

30 wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^bheterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

R⁴ represents hydrogen or an optionally substituted alkyl;

R⁵ represents hydrogen or an optionally substituted alkyl;

R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl,

35 optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted

SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR⁷;

R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

5 R⁸ and R⁹ independently represent hydrogen, chloro, fluoro, CF₃, alkoxy or alkyl;

Q^a and Q^b are independently selected from hydrogen and CH₃; and

when A is a 6-membered ring the R¹ substituent and cyclohexene ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R¹ substituent and cyclohexene ring are attached to

10 substitutable carbon atoms 1,2- or 1,3- relative to each other, or derivatives thereof.

Suitably A includes optionally substituted pyridyl.

15 Optional substituents for A include up to four substituents, preferably 0 or 1 substituent, independently selected from halogen, NR⁵R⁶, NR⁵COC₁₋₆alkyl, NR⁵SO₂C₁₋₆alkyl, OR⁵, optionally substituted C₁₋₄alkyl, e.g. CH₃ and CF₃, and NR¹⁰R¹¹ wherein R¹⁰ and R¹¹ together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, wherein R⁵ and R⁶ are as defined

20 above. Preferably optional substituents for A are selected from halogen, NH₂, NHC₁₋₄alkyl, NHCOC₁₋₄alkyl, and optionally substituted C₁₋₄alkyl, e.g. CH₃ and CF₃.

When B is pyridyl, preferably the pyridine N atom is situated adjacent to the ring carbon carrying either the cyclohexene or Z substituent.

25

In one aspect B is phenyl.

Preferably Z is O.

30 Suitably R¹ includes CO₂H, CONR⁵R⁶ e.g. CONHSO₂phenyl, CH₂CO₂H, SO₂C₁₋₆alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, or tetrazolyl. A particular example of R¹ is CO₂H.

Particular examples of R^{2a} and R^{2b} include hydrogen, halo, optionally substituted C₁₋₆alkyl, e.g. CH₃ and CF₃, optionally substituted C₁₋₆alkoxy, and CN. Preferably R^{2a} and R^{2b} are

35 independently selected from hydrogen, halo and CF₃.

Preferably R^{2a} is hydrogen. Preferably R^{2b} is positioned 1,4-relative to the Z substituent and 1,3 -relative to the cyclohexene ring.

40 Suitably R⁴ includes hydrogen or C₁₋₄alkyl. Preferably R⁴ is hydrogen.

Suitably R⁵ includes hydrogen or C₁₋₄alkyl.

Suitably R^6 includes hydrogen, C_{1-4} alkyl or SO_2 phenyl.

Suitably R^7 include hydrogen or C_{1-4} alkyl.

- 5 Suitably R^8 and R^9 include CH_3 or hydrogen. Preferably R^8 and R^9 are hydrogen.

Suitably R^x when an optionally substituted alkyl group include C_{1-8} alkyl.

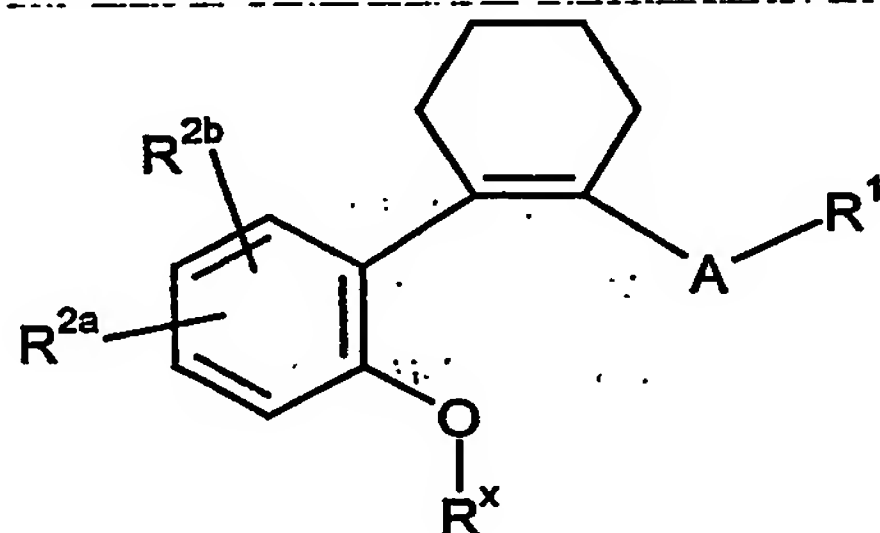
- 10 Suitably R^x include CH_2 phenyl optionally substituted by one, two or three, preferably one or two substituents, selected from Cl, Br, F, CF_3 , C_{1-4} alkyl and OC_{1-4} alkyl.

An example of Q^a is hydrogen.

An example of Q^b is hydrogen.

15

A certain group of compounds of formula (I) are compounds of formula (Ia):



(Ia)

wherein:

- 20 A is an optionally substituted 5- or 6- membered heterocyclyl ring;
 R^1 is CO_2H ;
 R^{2a} and R^{2b} are independently hydrogen, halo, optionally substituted C_{1-4} alkyl e.g. CH_3 and CF_3 , or optionally substituted C_{1-4} alkoxy;
 R^x is optionally substituted CH_2 -aryl;
 wherein when A is a 6-membered ring the R^1 substituent and cyclohexene ring are
 25 attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring the R^1 substituent and cyclohexene ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other,
 or derivatives thereof
- 30 In one aspect A is an optionally substituted 6-membered heterocyclyl ring, e.g. optionally substituted pyridyl.

Preferably R^{2a} is hydrogen.

- 35 Preferably R^{2b} represents hydrogen, halogen, or CF_3 .

Preferably R^{2b} is positioned 1,4- relative to the OR^x substituent and 1,3- relative to the cyclohexene ring.

- 5 Preferably R^x is CH_2 -phenyl optionally substituted by one, two or three substituents selected from halogen and CF_3 .

In one aspect when A is pyridyl the N atom is positioned 1,2- relative to the cyclohexene ring.

10

Compounds of formula (I) include:

6-[2-(5-chloro-2-[(4-fluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid;

15

6-[2-(5-chloro-2-[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid; and

6-[2-(5-chloro-2-[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid; and derivatives thereof.

20

Preferably compounds are selective for EP_1 over EP_3 . More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP_1 over EP_3 .

Derivatives of the compounds of formula (I) include pharmaceutically acceptable derivatives.

25

The invention is described using the following definitions unless otherwise indicated.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I).

30

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

35

It will be appreciated that, for pharmaceutical use, the salts referred to above will be pharmaceutically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the pharmaceutically acceptable salts thereof.

40

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts"

refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

The terms "halogen" or "halo" are used to represent fluorine, chlorine, bromine or iodine.

The term "alkyl" as a group or part of a group means a straight, branched or cyclic chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof such as cyclohexylmethyl and cyclopentylmethyl. Unless otherwise defined, preferably "alkyl" is C₁₋₈alkyl, more preferably "alkyl" is C₁₋₆alkyl.

The term "alkoxy" as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group. Preferably "alkoxy" is C₁₋₆ alkoxy.

5

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon to carbon double bond.

10

Preferably "alkenyl" is C₂₋₆alkenyl. C₂₋₆alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

15

The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents. Examples of 5-membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

20

The term "aryl" as a group or part of a group means a 5- or 6-membered aromatic ring, for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. An aryl group may be optionally substituted by one or more substituents, for example up to 4, 3 or 2 substituents. Preferably the aryl group is phenyl.

25

30

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents, for example up to 3 or up to 2 substituents. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothieryl, indolyl, and indazolyl.

35

40

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl,

quinoxaliny, quinazoliny, pyridopyraziny, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

5 When the heteroatom nitrogen replaces a carbon atom in an alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group, the nitrogen atom will, where appropriate, be substituted by one or two substituents selected from hydrogen and C₁₋₈alkyl, preferably hydrogen and C₁₋₆alkyl, more preferably hydrogen.

10 Optional substituents for alkyl or alkenyl groups unless hereinbefore defined include OH, CO₂R⁴, NR⁴R⁵, (O), -OC₁₋₆alkyl or halo e.g. Cl, Br or F, wherein R⁴, and R⁵ are as hereinbefore defined for compounds of formula (I). An alkyl or alkenyl group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents. Particular substituted alkyl groups include those substituted by one or more fluorines e.g. CH₂F, CHF₂, CF₃, C₂F₅ etc, especially CF₃.

15

Optional substituents for alkoxy groups unless hereinbefore defined include OH, and halo e.g. Cl, Br or F. An alkoxy group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents. Particular substituted alkoxy groups include those substituted by one or more fluorines e.g. OCH₂F, OCHF₂, OCF₃, OC₂F₅ etc.

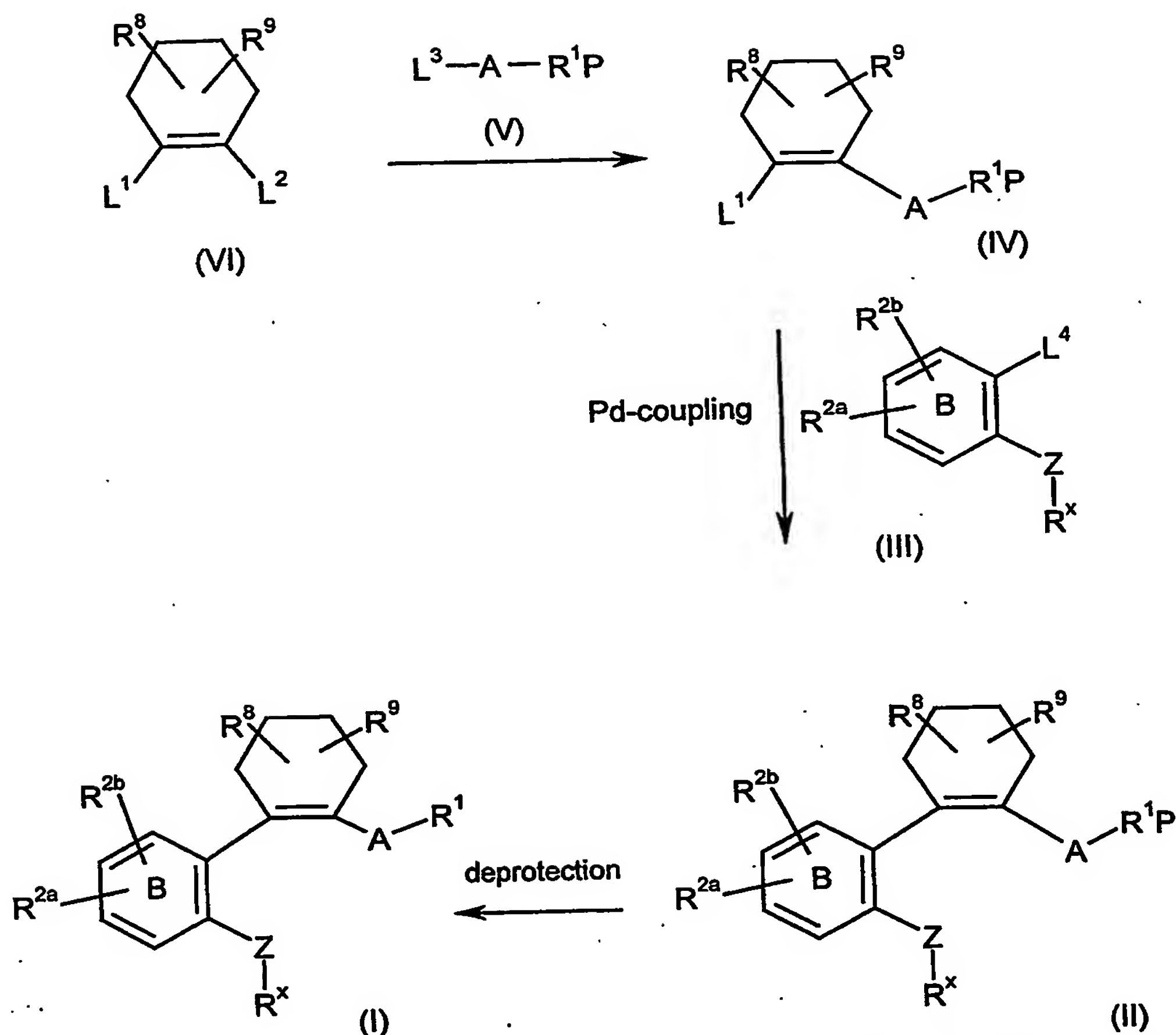
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Unless otherwise defined, optional substituents for aryl, heteroaryl or heterocyclyl moieties as a group or part of a group are selected from optionally substituted C₁₋₆alkyl, optionally substituted C₁₋₆alkoxy and halogen.

25

Compounds of formula (I) can be prepared as set forth in the following schemes and in the examples. The following processes form another aspect of the present invention.

For example, compounds of formula (I) may be prepared by the general route below:



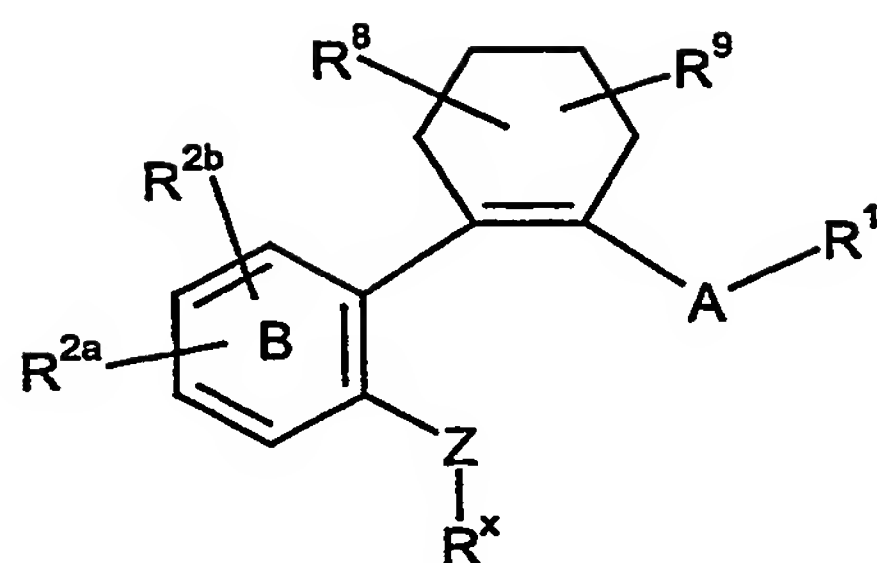
wherein L^1 , L^2 , are leaving groups for example halo, or triflate; L^3 and L^4 are activating groups, for example boronic acid; P is an optional protecting group; and A, B, R^1 , R^{2a} , R^{2b} , R^8 , R^9 , Z and R^x are as defined for compounds of formula (I). L^1 can be converted to L^{1a} , and L^2 can be converted to L^{2a} wherein L^{1a} and L^{2a} are activating groups for example a boronic acid, and in this situation L^3 and L^4 can be halo or triflate.

When R^1 is CO_2H examples of P include methyl, ethyl or substituted benzyl esters.

- 10 Suitable reaction conditions for the deprotection of a compound of formula (II) include heating in ethanolic sodium hydroxide solution.

- 15 Suitable reaction conditions for the reaction of a compound of formula (VI) with a boronic acid of formula (V, L^3 is $-\text{B}(\text{OH})_2$), or a compound of formula (IV) with a boronic acid of formula (III, L^4 is $-\text{B}(\text{OH})_2$) include heating with tetrakis(triphenylphosphine)palladium (0) and an inorganic base, for example potassium carbonate, in a solvent, e.g. ethylene glycol dimethyl ether (DME), toluene and ethanol, preferably in a ratio of 1:1.

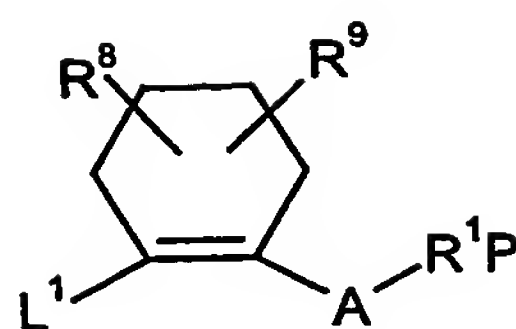
- 20 Accordingly the present invention also provides a process for the preparation of a compound of formula (i) or a derivative thereof:



(I)

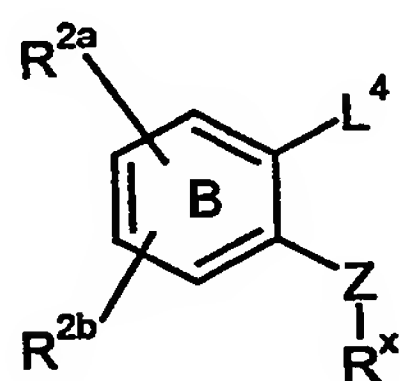
wherein:

- A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;
- B represents a phenyl or pyridyl ring;
- Z represents O, S, SO, or SO₂;
- R¹ represents CO₂H, CN, CONR⁵R⁶, CH₂CO₂H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO₂alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;
- R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶ or optionally substituted heteroaryl;
- R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR⁴, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^bheterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;
- R⁴ represents hydrogen or an optionally substituted alkyl;
- R⁵ represents hydrogen or an optionally substituted alkyl;
- R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR⁷;
- R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
- R⁸ and R⁹ independently represent hydrogen, chloro, fluoro, CF₃, alkoxy or alkyl;
- Q^a and Q^b are independently selected from hydrogen and CH₃; and
- when A is a 6-membered ring the R¹ substituent and cyclohexene ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R¹ substituent and cyclohexene ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
- comprising:
- reacting a compound of formula (IV):



(IV)

wherein R^8 , R^9 , A, and R^1 are as hereinbefore defined above for a compound of formula (I), L^1 is a leaving group and P is an optional protecting group;
 5 with a compound of formula (III):



(III)

10 wherein R^{2a} , R^{2b} , B, Z, and R^x are as hereinbefore defined above for a compound of formula (I) and L^4 is an activating group;

and where required converting:

one group A to another group A, and/or

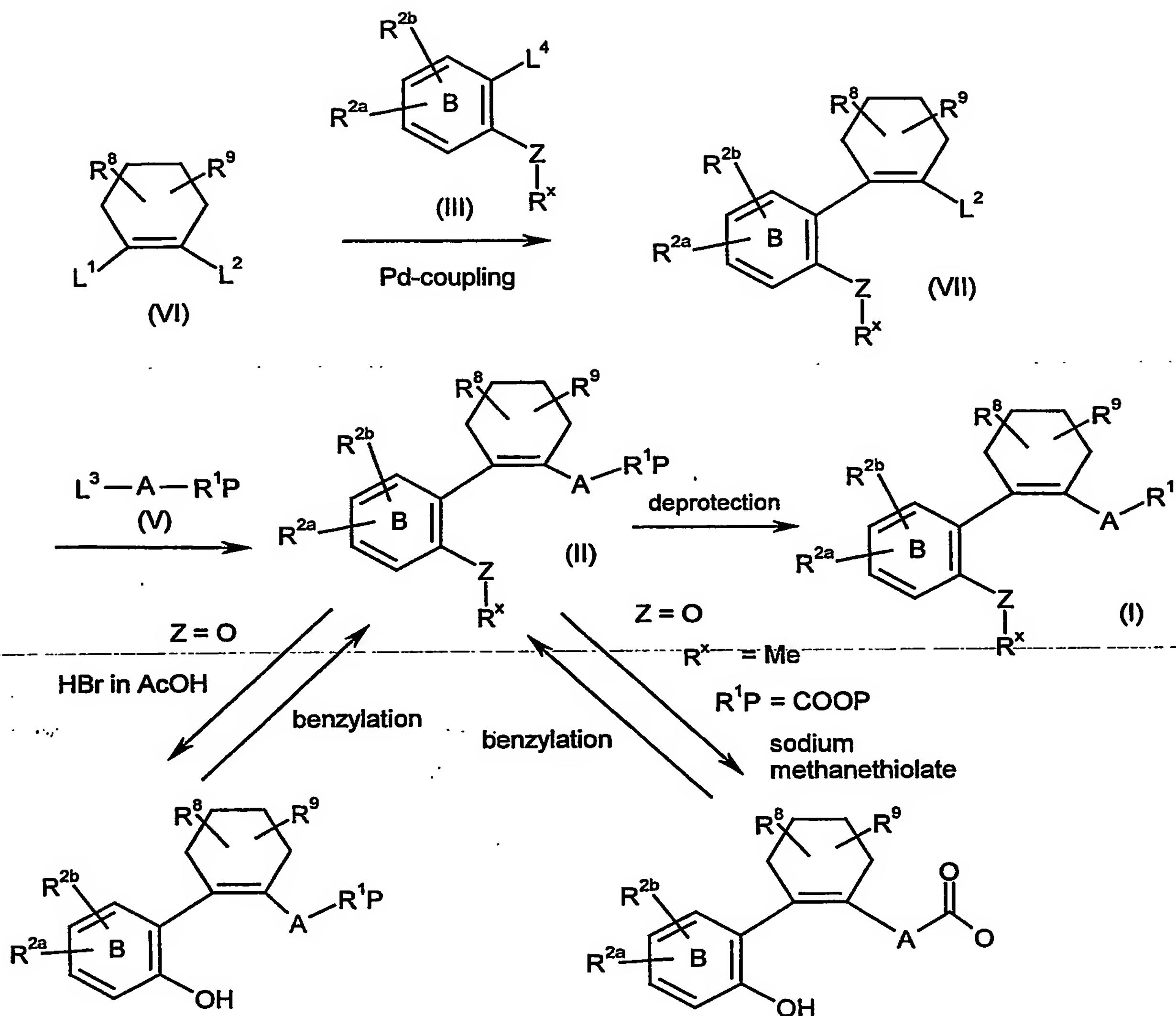
one group R^x to another group R^x ;

15 and where required carrying out the following optional steps in any order:
 effecting deprotection; and/or

converting one group R^1 to another group R^1 ; and/or

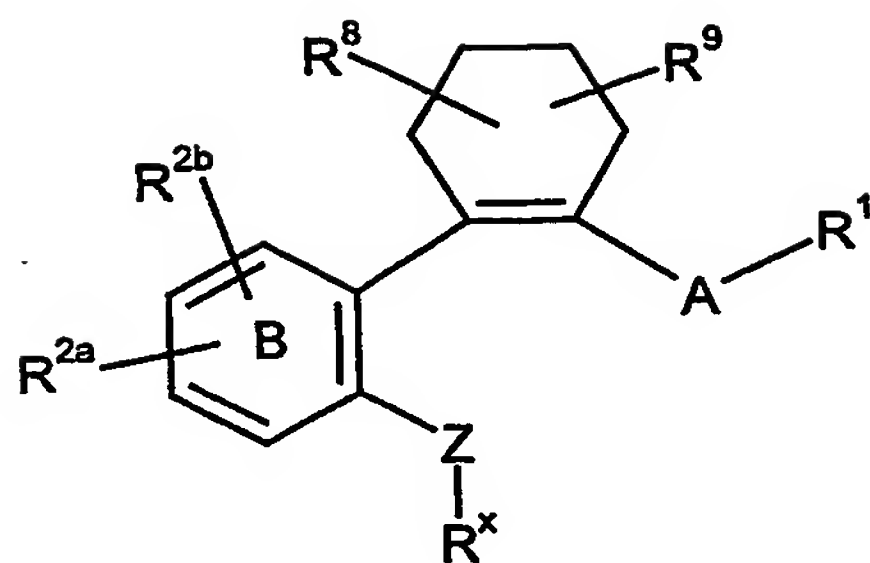
forming a derivative of the compound of formula (I) so formed.

20 Alternatively compounds of formula (I) may be prepared according to the route described below:



wherein L^1 , L^2 , L^3 , L^4 and P are as defined above, and A , B , R^1 , R^{2a} , R^{2b} , R^8 , R^9 , Z , and R^x are as defined for compounds of formula (I). L^1 can be converted to L^{1a} , and L^2 can be converted to L^{2a} wherein L^{1a} and L^{2a} are activating groups for example a boronic acid, and in this situation L^3 and L^4 can be halo or triflate.

Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:



(I)

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

5 B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO₂;

R¹ represents CO₂H, CN, CONR⁵R⁶, CH₂CO₂H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO₂alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted

10 heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR⁴, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^bheterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

15 R⁴ represents hydrogen or an optionally substituted alkyl;

R⁵ represents hydrogen or an optionally substituted alkyl;

20 R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR⁷;

25 R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

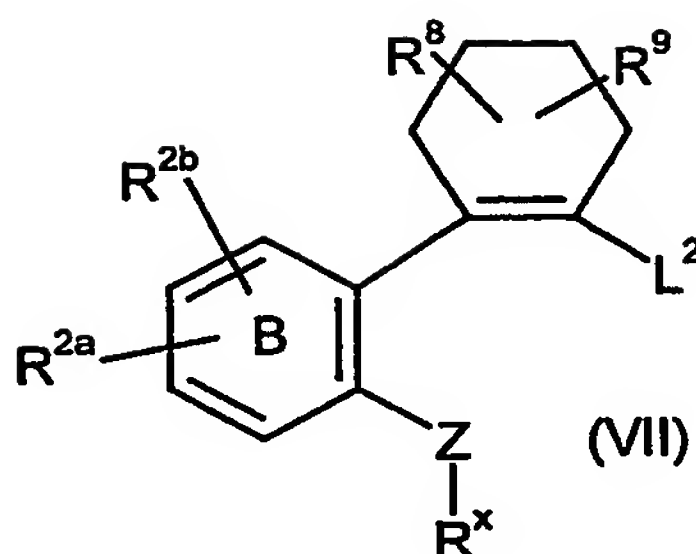
R⁸ and R⁹ independently represent hydrogen, chloro, fluoro, CF₃, alkoxy or alkyl;

Q^a and Q^b are independently selected from hydrogen and CH₃; and

30 when A is a 6-membered ring the R¹ substituent and cyclohexene ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R¹ substituent and cyclohexene ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;

comprising;

reacting a compound of formula (VII):



wherein R^{2a} , R^{2b} , R^8 , R^9 , B, and R^x are as hereinbefore defined above for a compound of formula (I), and L^2 is a leaving group;

5 with a compound of formula (V):



(V)

wherein R^1 , and A are as hereinbefore defined above for a compound of formula (I); L^3 is

- 10 an activating group and P is an optional protecting group;
and where required converting:
one group A to another group A, and/or
one group R^x to another group R^x ;
and where required carrying out the following optional steps in any order:
15 effecting deprotection; and/or
converting one group R^1 to another group R^1 ; and/or
forming a derivative of the compound of formula (I) so formed.

- 20 It will be appreciated that certain substituents in intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art.

- A group R^1 may be converted to another group R^1 by use of conventional organic transformations known to those skilled in the art. For example $R^1 = CO_2H$ may be
25 converted to an amide, e.g. $CONHCQ^aQ^b\text{aryl}$ or $CONHCQ^aQ^b\text{heteroaryl}$ wherein Q^a and Q^b are selected from hydrogen and CH_3 , by conventional methods for the preparation of amides as described in, for example, Richard Larock, *Comprehensive Organic Transformations*, 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

- 30 Cyclohexene derivatives of formula (VI), boronic acids of formula (III) and (V), and tetrakis(triphenylphosphine)palladium (0) are commercially available, or readily prepared by methods known to those skilled in the art.

- The preparation and reactions of boronic acids of formula (III) and formula (V) is reviewed
35 in Suzuki *et al*, *Synth. Commun.*, 1981, 11, 513; Martin *et al*, *Acta. Chim. Scand.*, 1993,

47, 221; and Miyaura *et al*, *Chem. Rev.*, 1995, 95, 2457. For example, 2-benzyloxy-5-chlorophenylboronic acid may be prepared from 2-benzyloxy-5-chloro-iodobenzene. 2-Benzyloxy-5-chloro-iodobenzene may be prepared from 4-chloro-2-iodoanisole by demethylation followed by benzylation according to known methods.

5

Certain substituents in any of the reaction intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art. Examples of substituents which may be converted include one group R^x to another group R^x ; and one substituent on a group A to another substituent on a group A.

10

Examples of such transformations include the reduction of a nitro group to give an amino group; alkylation and amidation of amino groups; hydrolysis of esters, alkylation of hydroxy and amino groups; and amidation and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example, Richard Larock, *Comprehensive Organic Transformations*, 2nd edition, Wiley-VCH, ISBN

15

0-471-19031-4.

20

For example, when R^x is p-methoxybenzyl, cleavage of the ether to give the phenol or pyridinol is carried out using, for example, using acid e.g. HCl/dioxane, HBr/acetic acid or using sodium methanethiolate. When R^x is methyl, cleavage of the ether to give the phenol is carried out using, for example, sodium methanethiolate. Cleavage of the ether to give a pyridinol is carried out in the presence of, for example, trifluoroacetic acid. Conversion to another R^x group, for example a substituted benzyl group, may be effected by reaction of the phenol or pyridinol with a suitable substituted benzyl bromide. The skilled person will appreciate that conversion of the protecting group P to another protecting group P may also occur under the reaction conditions used. When R^x is benzyl, cleavage of the ether to give the phenol or pyridinol may be carried out by hydrogenation according to known methods e.g. H_2 -Pd/C or NH_4CO_2H -Pd/C. The resulting phenol or pyridinol can then be converted to another group R^x as described above.

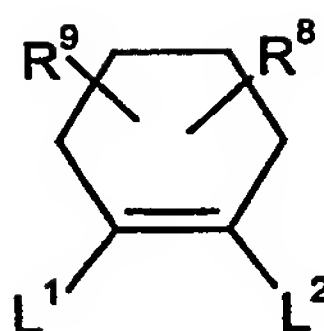
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It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

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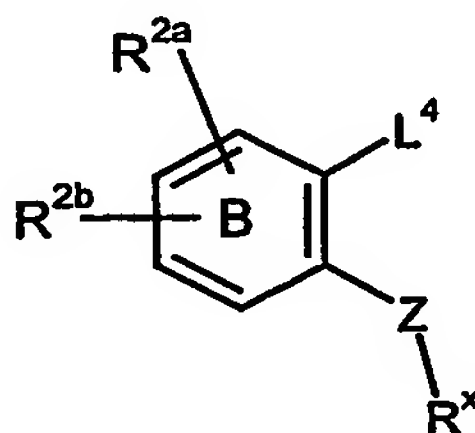
Cyclohexene intermediates of the formula (VI):



(VI)

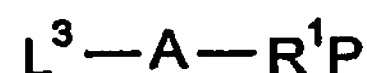
wherein L^1 , L^2 are as defined above, and R^8 and R^9 are as hereinbefore defined for compounds of formula (I) are commercially available or may be readily prepared according to known methods.

Compounds of the formula (III):



wherein L^4 is as hereinbefore defined, R^{2a} , R^{2b} , Z , B and R^x are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available pyridinols, anisoles or phenols using methods as described in the examples.

Compounds of the formula (V):



wherein L^3 and P are as defined above and R^1 and A are as hereinbefore defined for compounds of formula (I) are commercially available or may readily be prepared, for example, from suitable halobenzoic acid esters according to known methods, for example using methods as described in the examples.

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the invention bind to the EP_1 receptor and are therefore useful in treating conditions mediated by the action of PGE_2 at EP_1 receptors.

In view of their ability to bind to the EP₁ receptor, the compounds of the invention may be useful in the treatment of the disorders that follow.

- 5 The compounds of formula (I) may be useful as analgesics. They are therefore useful in the treatment or prevention of pain.

10 The compounds of formula (I) may be used as an analgesic to treat acute pain, chronic pain, neuropathic pain, inflammatory pain, visceral pain, pain associated with cancer and fibromyalgia, pain associated with migraine, tension headache and cluster headaches, and pain associated with functional bowel disorders, non-cardiac chest pain and non-ulcer dyspepsia.

15 The compounds of formula (I) may be useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis; osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections; such as the common cold; rheumatic fever; pain associated with functional bowel disorders
20 such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea. The compounds of the invention may also be useful in the treatment of visceral pain.

25 The compounds of the invention may be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the
30 brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions
35 are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased
40 sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal,

cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of fever.

5

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthesia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, tendinitis, bursitis, and Sjogren's syndrome.

20

The compounds of formula (I) may also be useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) may also be effective in increasing the latency of HIV infection.

25

The compounds of formula (I) may also be useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).

30

The compounds of formula (I) may also be useful for the preparation of a drug with diuretic action.

The compounds of formula (I) may also be useful in the treatment of impotence or erectile dysfunction.

35

The compounds of formula (I) may also be useful in the treatment of bone disease characterised by abnormal bone metabolism or resorption such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculus, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

40

The compounds of formula (I) may also be useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

- 5 The compounds of formula (I) may also be useful in the treatment of cardiovascular diseases such as hypertension or myocardial ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).
- 10 The compounds of formula (I) may also be useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with
- 15 intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment. The compounds of formula (I) are also useful in the treatment of neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass,
- 20 traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) may also be useful in the treatment of tinnitus.

- 25 The compounds of formula (I) may also be useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine. The compounds of formula (I) are also useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy,
- 30 macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

- 35 The compounds of formula (I) may also be useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

- 40 According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.

5 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE₂ at EP₁ receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

10 According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

15 According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

20 According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.

25 According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

30 According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

35 The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

40

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

- 5 The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their
10 pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

- 15 For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

- For parenteral administration, the pharmaceutical composition may be given as an
20 injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.
25 Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

- The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the
30 compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

- The EP₁ receptor compounds for use in the instant invention may be used in combination
35 with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A₁ receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor
40 antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; 5HT₁ agonists, such as triptans,

for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor modulators, for example modulators of the NR2B subtype; EP₄ receptor ligands; EP₂ receptor ligands; EP₃ receptor ligands; EP₄ antagonists; EP₂ antagonists and EP₃ antagonists; cannaboid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

10 Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

15 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

20 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

25 When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

30 A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day

35 The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

40 The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

10 The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

EXAMPLES

Abbreviations:

15 Bn (benzyl), Bu, Pr, Me, Et (butyl, propyl, methyl ethyl), DMSO (dimethyl sulfoxide), DCM (dichloromethane), DME (ethylene glycol dimethyl ether), DMF (N,N-dimethylformamide), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), EtOAc (ethyl acetate), EtOH (ethanol), HPLC (High pressure liquid chromatography), LCMS (Liquid chromatography/Mass spectroscopy), MDAP (Mass Directed Purification), MeOH (methanol), NMR (Nuclear Magnetic Resonance (spectrum)), Ph (phenyl), pTSA (para-toluene sulphonic acid), SPE (Solid Phase Extraction), TBAF (tetrabutylammonium fluoride), THF (tetrahydrofuran), s, d, t, q, m, br (singlet, doublet, triplet, quartet, multiplet, broad.)

20

25 LCMS

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5µl
- 30 • Temp: RT
- UV Detection Range: 215 to 330nm
-

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
B: 95% Acetonitrile + 0.05% Formic Acid

| Gradient: Time | A% | B% |
|----------------|-----|-----|
| 0.00 | 100 | 0 |
| 0.70 | 100 | 0 |
| 4.20 | 0 | 100 |
| 5.30 | 0 | 100 |
| 5.50 | 100 | 0 |

35 Mass Directed Autopreparation

Hardware:

Waters 600 gradient pump

Waters 2767 inject/collector

5 Waters Reagent Manager

Micromass ZMD mass spectrometer

Gilson Aspec - waste collector

Gilson 115 post-fraction UV detector

Software :

10 Micromass Masslynx version 4.0

Column

The column used is typically a Supelco LCABZ++ column whose dimensions are 20mm internal diameter by 100mm in length. The stationary phase particle size is 5µm.

Solvents:

15 A: Aqueous solvent = Water + 0.1% Formic Acid

B: Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid

Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate

Needle rinse solvent = MeOH: Water: DMSO 80:10:10

20 The method used depends on the analytical retention time of the compound of interest.

15-minute runtime, which comprises a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.

MDP 1.5-2.2 = 0-30%B

MDP 2.0-2.8 = 5-30% B

25 MDP 2.5-3.0 = 15-55%B

MDP 2.8-4.0 = 30-80% B

MDP 3.8-5.5 = 50-90% B

Flow-rate:

flow rate 20ml/min.

30

Intermediates**a) 2-Benzyloxy-5-chloriodobenzene**

35

A mixture of 5-chloro-2-iodophenol (20g, 78.59 mmol), potassium carbonate (20g, 144.93 mmol) and benzyl bromide (14.78g, 86.45 mmol) in acetone (200ml) was stirred and refluxed for 3 hours. The resulting mixture was cooled, filtered, evaporated to dryness, dissolved in iso-hexane and left to crystallise. There was obtained 25.74g of light brown solid.

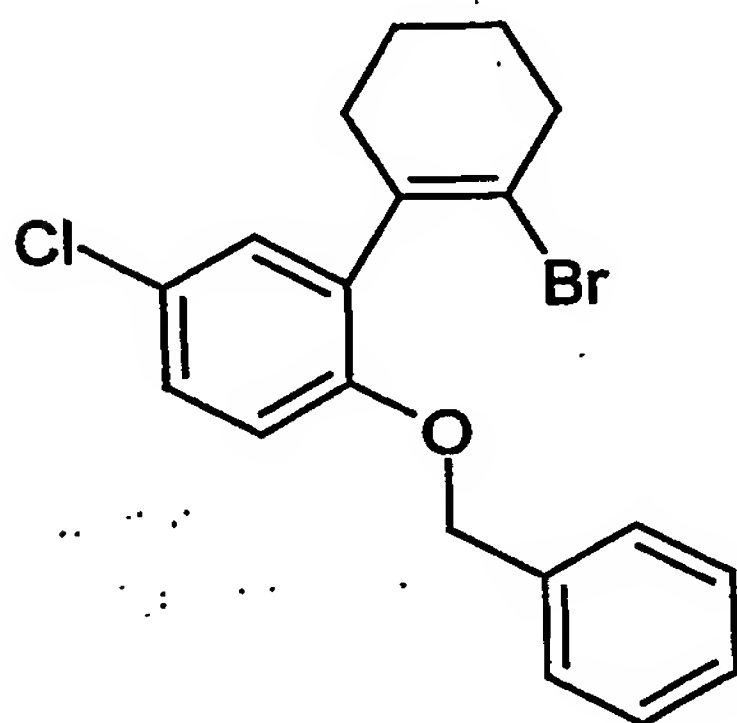
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¹H NMR (CDCl₃) δ: 5.13 (s, 2H), 6.76 (d, 1H), 7.22-7.48 (m, 6H), 7.77 (d, 1H).
b) 2-Benzyloxy-5-chlorophenylboronic acid

A solution of 2M isopropylmagnesium chloride in diethyl ether (46.5ml, 93 mmol) was added over 20 minutes to a solution of 2-benzyloxy-5-chloriodobenzene (16.02g, 46.5 mmol) in dry THF (150ml) at -40°C under nitrogen. After stirring for 1 hour at -40°C the mixture was cooled to -78°C and trimethyl borate (9.67g, 93 mmol) was added over 5 minutes. The resulting mixture was allowed to warm to room temperature and 2M hydrochloric acid (200ml) was added and stirred vigorously for 15 minutes. The organic phase was separated, dried (magnesium sulphate), evaporated to dryness and triturated with iso-hexane to give 11.9g of off-white solid.

LC/MS: Rt 3.4, [2MH⁺] 637.3

c) 2-(2-Bromo-1-cyclohexen-1-yl)-4-chloro-1-[(phenylmethyl)oxy]benzene



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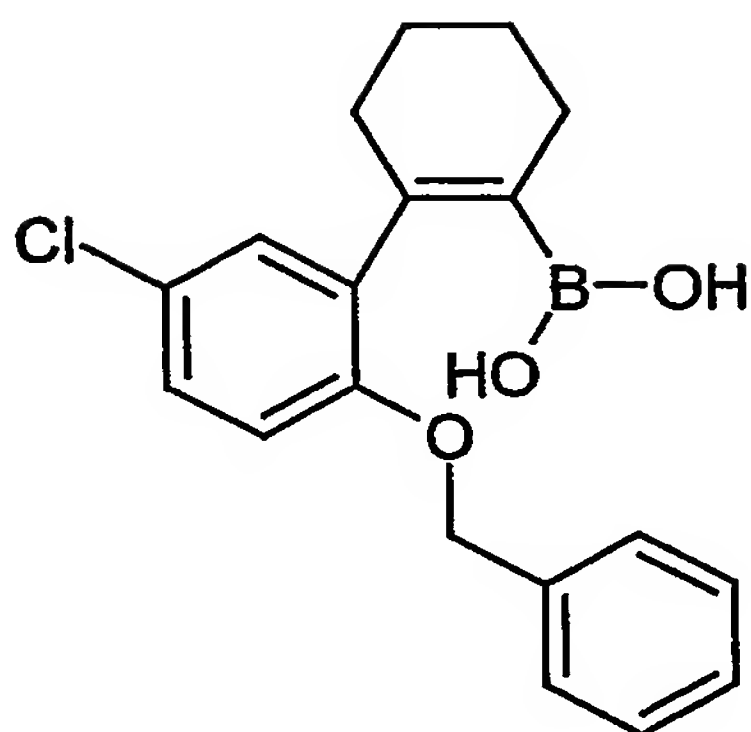
A mixture of 2-benzyloxy-5-chlorophenylboronic acid (2.983g, 11.36 mmol), 1,2-dibromocyclohexene (10.91g, 45.46 mmol), potassium carbonate (13.8g, 100 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.158g, 1 mmol) in 1:1 toluene/ethanol (250ml) was stirred and heated at 90°C under nitrogen for 4 hours. After cooling the mixture was diluted with diethyl ether and water and the organic layer separated, dried (magnesium sulphate) and evaporated to dryness. The residue was chromatographed on silica eluting with ethyl acetate/iso-hexane (1:49) then rechromatographed eluting with dichloromethane/iso-hexane (1:9) and recrystallised from iso-hexane to give 638mg of white crystals.

^1H NMR (d_6 DMSO) δ : 1.55-1.80 (m, 4H), 2.12-2.22 (m, 1H), 2.30-2.41 (m, 1H), 2.51-2.60 (m, 2H), 5.13 (s, 2H), 7.07(d, 1H), 7.10 (d, 1H), 7.28-7.43 (m, 6H).

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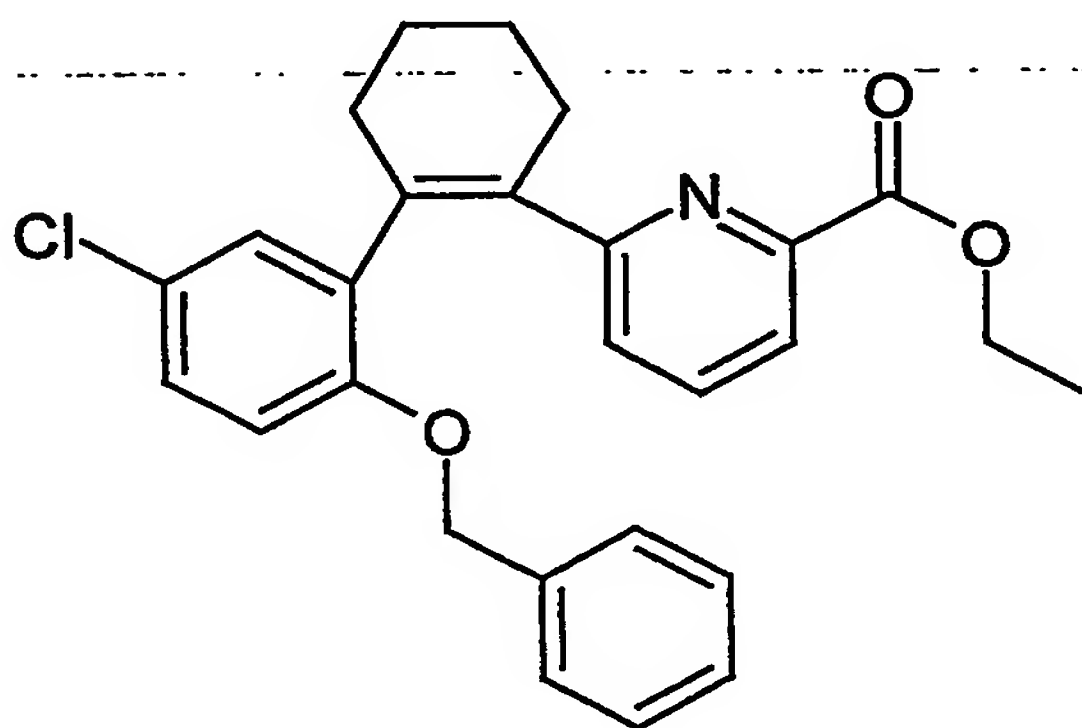
d) (2-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}-1-cyclohexen-1-yl)boronic acid

30



1.6M butyllithium in hexanes (0.21ml, 0.34 mmol) was added to a stirred solution of 2-(2-bromo-1-cyclohexen-1-yl)-4-chloro-1-[(phenylmethyl)oxy]benzene (126mg, 0.33mmol) in dry THF (5ml) at -78C under nitrogen and stirred for 15 minutes. Triisopropyl borate (124mg, 0.66 mmol) was added and the mixture allowed to warm to room temperature and 2M hydrochloric acid (5ml) was added. The resulting mixture was stirred vigorously for 10 minutes and the organic layer separated, dried (magnesium sulphate) evaporated and chromatographed on silica eluting with ethyl acetate/iso-hexane (1:4) to give 44mg of colourless gum.
LC/MS: Rt 3.73, [2MH+] 689.4

e) Ethyl 6-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1-cyclohexen-1-yl)-2-pyridinecarboxylate



20

A mixture of (2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1-cyclohexen-1-yl)boronic acid (44mg, 0.128 mmol), 6-bromopicolinic acid ethyl ester (30mg, 0.13mmol), potassium carbonate (138mg, 1mmol) and tetrakis(triphenylphosphine)palladium(0) (12mg, 0.01 mmol) in 1:1 toluene/ethanol (3ml) was stirred and heated at 90C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic

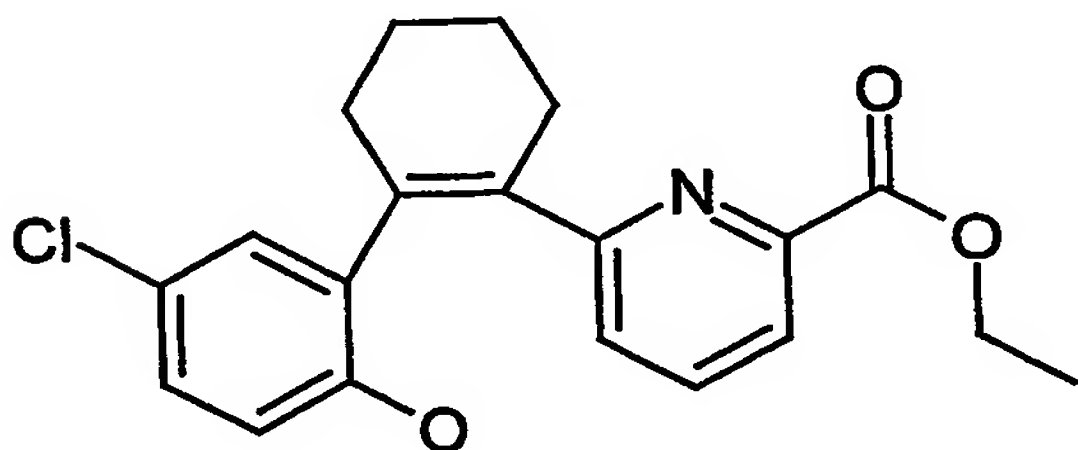
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layer separated, dried (magnesium sulphate) and evaporated to dryness then chromatographed on silica eluting with ethyl acetate/iso-hexane (1:9) to give 35mg of colourless gum.

LC/MS: Rt 4.16, [MH⁺] 448.4, 450.4

5

f) Ethyl 6-[2-(5-chloro-2-hydroxyphenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylate



10

Ethyl 6-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1-cyclohexen-1-yl)-2-pyridinecarboxylate (310mg, 0.69 mmol) was dissolved in acetic acid (1ml) and 48% hydrogen bromide in acetic acid (5ml) and left at room temperature for 1 hour then poured into diethyl ether/water and basified with potassium carbonate. The organic layer was separated, dried (magnesium sulphate) and chromatographed on silica eluting with ethyl acetate/iso-hexane (3:17) and the resulting mixture dissolved in ethanol (5ml) and 60% sodium hydride (2mg) added. After leaving overnight at room temperature the solution was diluted with water/diethyl ether, acidified with acetic acid and the organic layer washed with saturated sodium bicarbonate solution, dried (magnesium sulphate) and evaporated to give 201 mg of colourless gum.

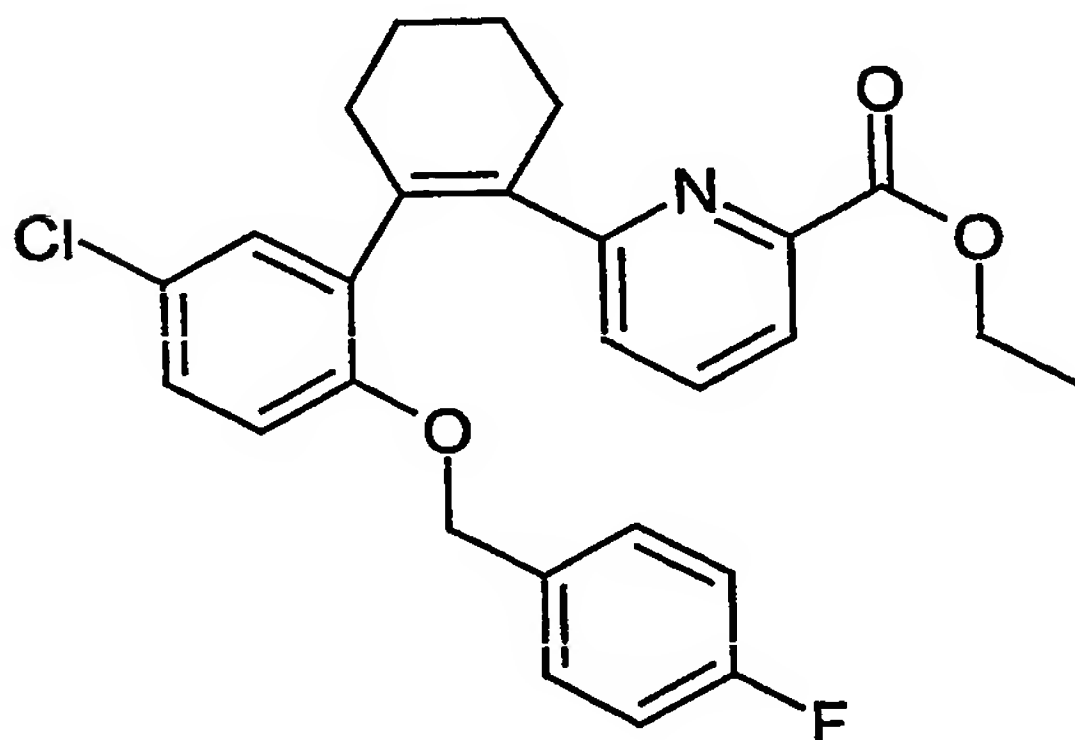
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LC/MS: Rt 3.56, [MH⁺] 358.4, 360.4

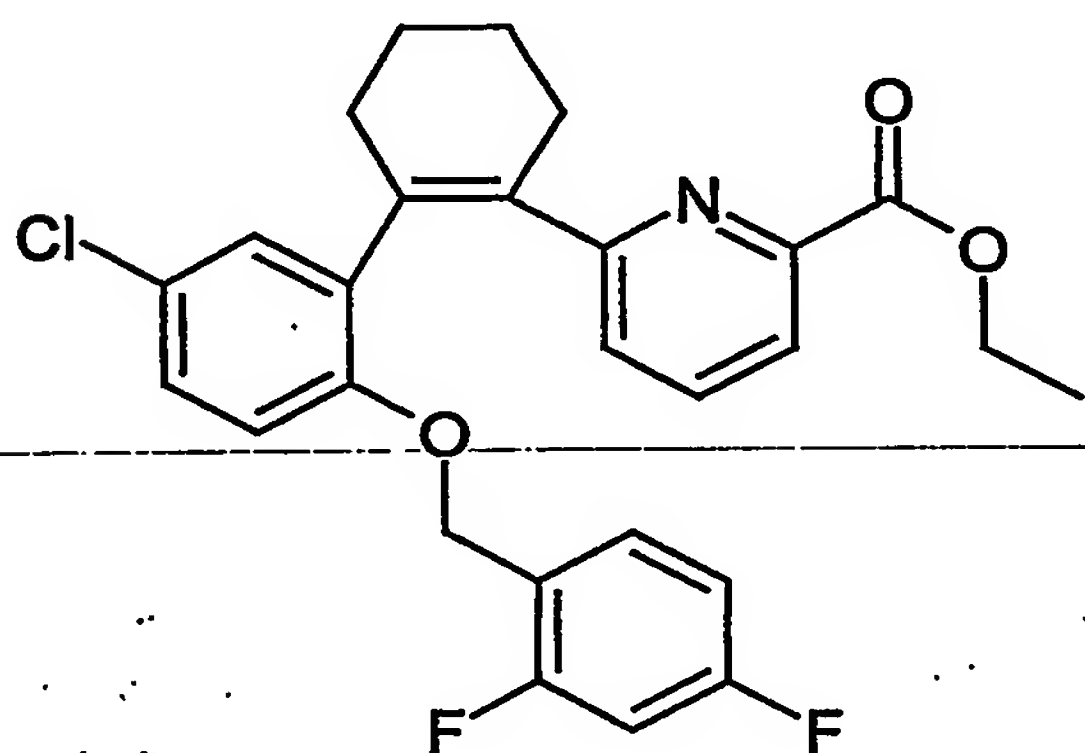
g) Ethyl 6-[2-(5-chloro-2-[(4-fluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylate

25



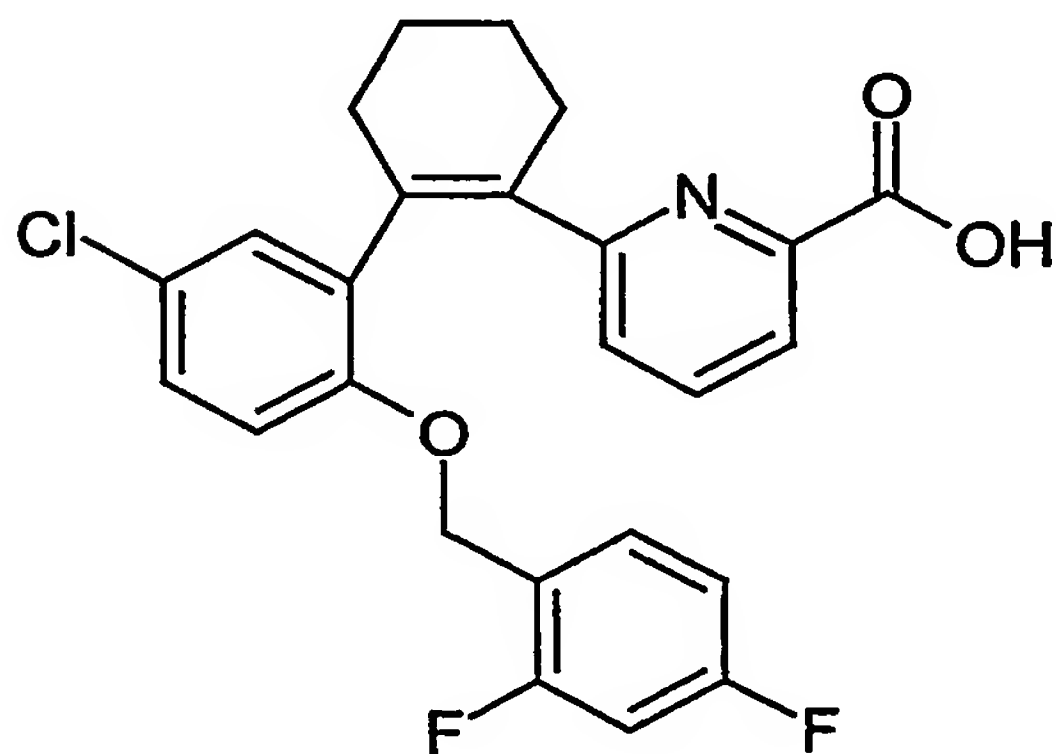
A mixture of ethyl 6-[2-(5-chloro-2-hydroxyphenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylate (100mg, 0.28mmol), 4-fluorobenzyl bromide (63mg, 0.33 mmol) and potassium carbonate (138 mg, 1mmol) in acetone (5ml) was stirred and refluxed for 3 hours. After cooling the mixture was filtered, evaporated and chromatographed on silica eluting with ethyl acetate/iso-hexane (1:9) to give 96mg of white solid.
LC/MS: Rt 4.17, [MH⁺] 466.4, 468.3

h) Ethyl 6-[2-(5-chloro-2-[[2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylate



Prepared as a white solid in the same manner as for ethyl 6-[2-(5-chloro-2-[[4-fluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylate but using 2,4-difluorobenzyl bromide instead of 4-fluorobenzyl bromide.
LC/MS: Rt 4.22, [MH⁺] 484.4, 486.3

Example 1
6-[2-(5-Chloro-2-[[2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid



Ethyl 6-[2-(5-chloro-2-[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylate (116mg, 0.24 mmol) was dissolved in ethanol (5ml) and 2M sodium hydroxide (1ml) and left at room temperature for 1 hour. The resulting solution was diluted with water/diethyl ether, acidified with acetic acid and the organic layer separated, dried (magnesium sulphate), toluene (10ml) added and evaporated to dryness. The residue was

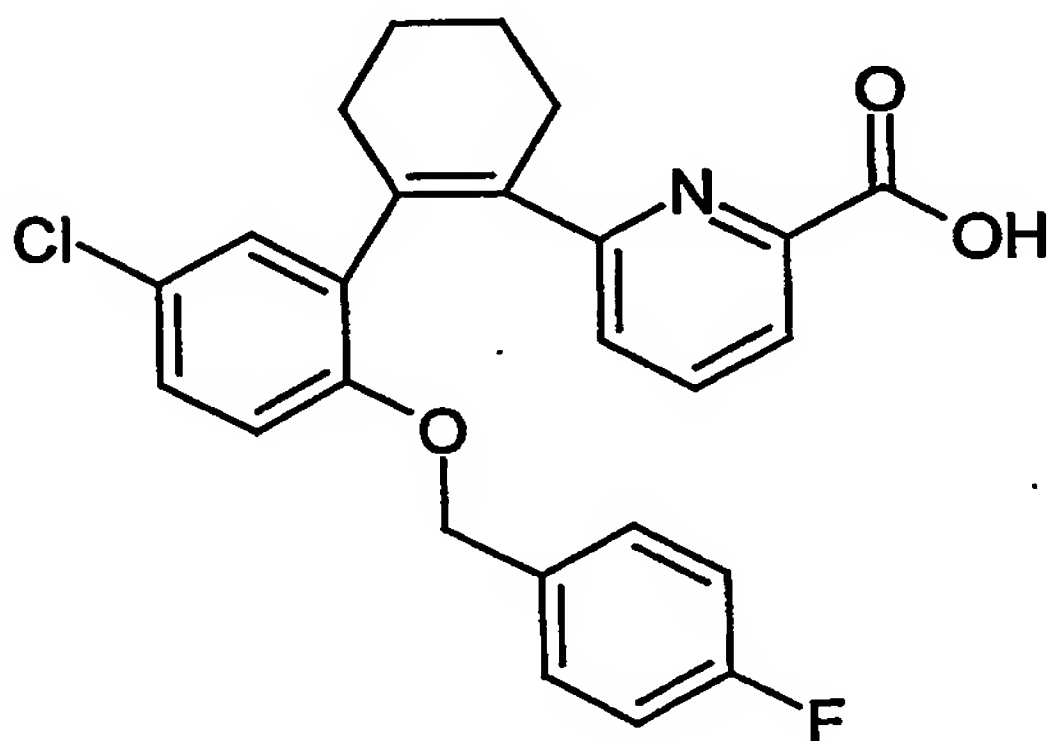
triturated with iso-hexane to give 79mg of white solid.

LC/MS: Rt 3.91, [MH⁺] 456.3, 458.3

¹H NMR (d₆ DMSO) δ: 1.60-1.82 (4H, br.m.), 2.05-2.85 (4H, br. m.), 5.11 (2H,s), 6.76 (1H,d), 6.88 (1H, dd), 7.08-7.19 (3H, m), 7.27-7.34 (1H, dt), 7.52-7.59 (2H, m), 7.25 (1H, d), 12.7-13.4 (1H, br. s.).

Example 2

6-[2-(5-Chloro-2-[(4-fluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid



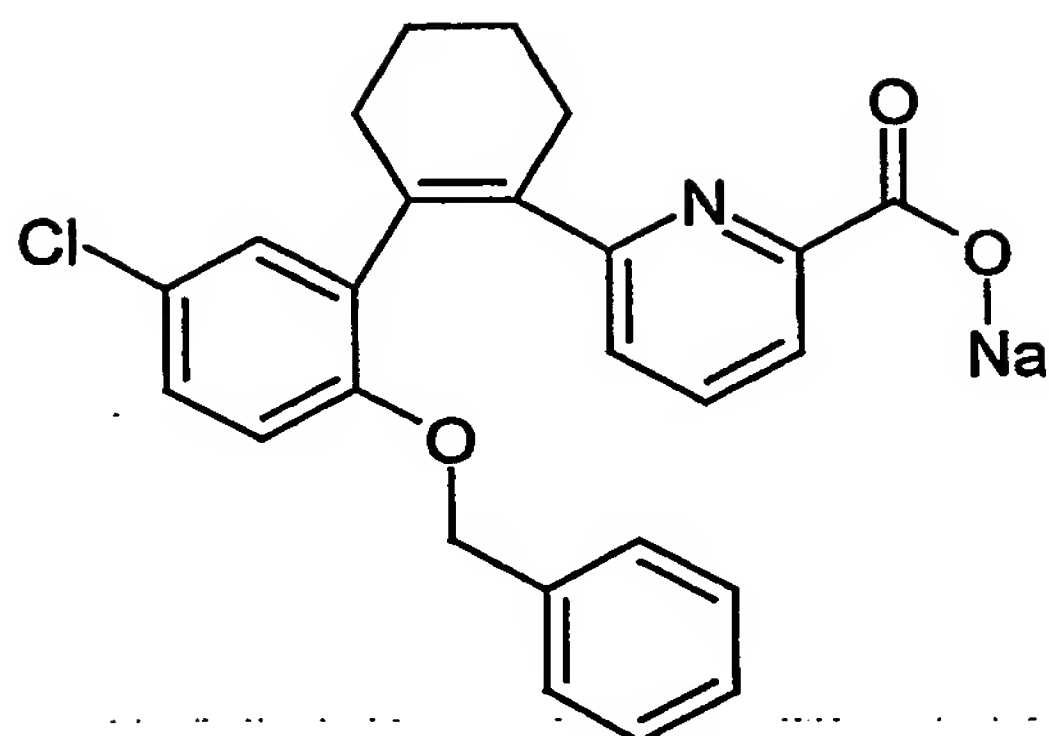
Ethyl 6-[2-(5-chloro-2-[(4-fluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylate (96mg, 0.21 mmol) was dissolved in ethanol (5ml) and 2M sodium hydroxide (1ml) and left at room temperature for 1 hour. The resulting solution was diluted with water/diethyl ether, acidified with acetic acid and the organic layer separated, dried (magnesium sulphate), toluene (10ml) added and evaporated to dryness. The residue was triturated with iso-hexane to give 72mg of white solid.

LC/MS: Rt 3.80, [MH⁺] 438.3, 440.4

¹H NMR (d₆ DMSO) δ: 1.69-1.83 (4H, m), 2.1-2.8(4H, br.m), 5.07 (2H,s), 6.79 (1H,d), 6.91 (1H, dd), 7.00 (1H, d), 7.16 (1H, dd), 7.20 (2H, t), 7.43 (2H, dd), 7.55 (1H, t), 7.72 (1H,d), 12.5-13.4 (1H, br.s.).

Example 3

6-(2-{5-Chloro-2-[(phenylmethyl)oxy]phenyl}-1-cyclohexen-1-yl)-2-pyridinecarboxylic acid sodium salt



5 Ethyl 6-(2-{5-chloro-2-[(phenylmethyl)oxy]phenyl}-1-cyclohexen-1-yl)-2-pyridinecarboxylate (60mg, 0.13 mmol) was dissolved in ethanol (5ml) and 2M sodium hydroxide (1ml) and left at room temperature for 1 hour. The resulting solution was diluted with water/diethyl ether, acidified with acetic acid and the organic layer separated, dried (magnesium sulphate), toluene (10ml) added and evaporated to dryness. The residue was dissolved in ethanol (2ml) and 2M sodium hydroxide (0.5ml) then diluted with ethyl acetate/water. The organic

layer was dried and evaporated to give 11mg of white solid.

10 LC/MS: Rt 3.83, [MH⁺] 420.4, 422.3

¹H NMR (d₆ DMSO) (50°C) δ: 1.66-1.79 (4H, m), 2.19-2.25 (2H, m), 2.46-2.54 (2H, m), 5.09 (2H, s), 6.75 (1H, d), 6.78 (1H, d), 6.93 (1H, d), 6.99 (1H, dd), 7.26-7.46 (6H, m), 7.75 (1H, d).

15 It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

20 The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The prostaglandin receptors investigated are DP, EP₁, EP₂, EP₃, EP₄, FP, IP and TP.

25 The ability of compounds to antagonise EP₁ & EP₃ receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ([Ca²⁺]_i) in response to activation of EP₁ or EP₃ receptors by the natural agonist hormone prostaglandin E₂ (PGE₂). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE₂ can mobilise. The net effect is to displace the

30 PGE₂ concentration-effect curve to higher concentrations of PGE₂. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of [Ca²⁺]_i produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected

using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

5 The human EP₁ or EP₃ calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP₁ or EP₃ cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10µg/ml puromycin.

10 For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in 15 order to assess the agonist properties of the compounds. Concentrations of PGE₂ are then added to the plate in order to assess the antagonist properties of the compounds.

20 The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE₂ (pIC₅₀) may then be estimated.

Binding Assay for the Human Prostanoid EP₁ Receptor

25 Competition assay using [³H]-PGE₂.

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E₂ ([³H]-PGE₂) for binding to the human EP₁ receptor.

30 This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP₁ cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10µg/ml puromycin and 10µM 35 indomethacin.

40 Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid (Na₂EDTA) and 10µM indomethacin for 5 min. The cells are isolated by centrifugation at 250xg for 5mins and suspended in an ice cold buffer such as 50 mM Tris, 1mM Na₂EDTA, 140mM NaCl, 10µM indomethacin (pH 7.4). The cells are homogenised using a Polytron tissue disrupter (2x10s burst at full setting), centrifuged at 48,000xg for 20mins and the pellet containing the membrane fraction is washed three times by suspension and

centrifugation at 48,000xg for 20mins. The final membrane pellet is suspended in an assay buffer such as 10mM 2-[N-morpholino]ethanesulphonic acid, 1mM Na₂EDTA, 10mM MgCl₂ (pH 6). Aliquots are frozen at -80°C until required.

- 5 For the binding assay the cell membranes, competing compounds and [³H]-PGE₂ (3nM final assay concentration) are incubated in a final volume of 100μl for 30 min at 30°C. All reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation counting in Packard TopCount scintillation counter.

The data are analysed using non linear curve fitting techniques (GraphPad Prism 3) to determine the concentration of compound producing 50% inhibition of specific binding (IC₅₀).

- 15 By application of these techniques, compounds of the examples had an antagonist pIC₅₀ value of between 7.0 and 9.5 at EP₁ receptors and pIC₅₀ value of < 6.0 at EP₃ receptors.

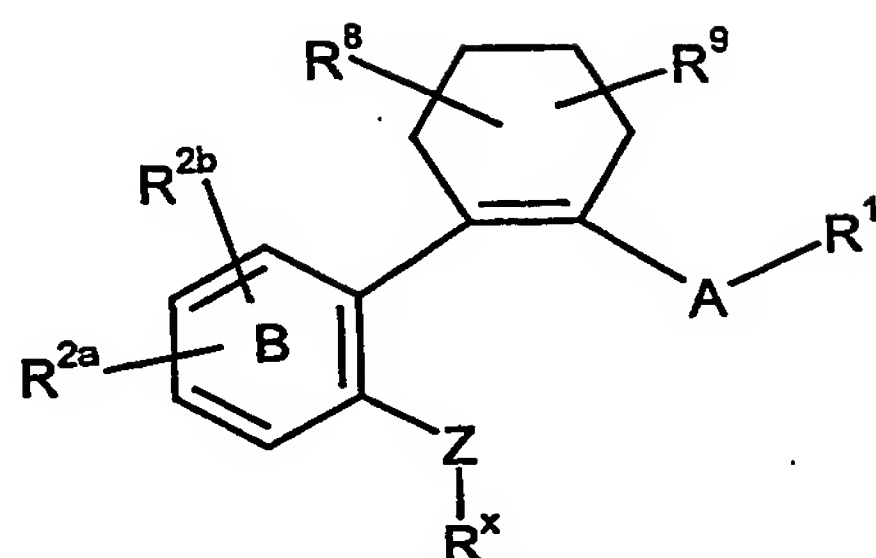
- 20 No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein.

- 25 They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

5

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

B represents a phenyl or pyridyl ring;

10 Z represents O, S, SO, or SO₂;

R¹ represents CO₂H, CN, CONR⁵R⁶, CH₂CO₂H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO₂alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, COalkyl; 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

15 R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR⁴, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^bheterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

R⁴ represents hydrogen or an optionally substituted alkyl;

R⁵ represents hydrogen or an optionally substituted alkyl;

25 R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR⁷;

R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

30 R⁸ and R⁹ independently represent hydrogen, chloro, fluoro, CF₃, alkoxy or alkyl;

Q^a and Q^b are independently selected from hydrogen and CH₃; and

when A is a 6-membered ring the R¹ substituent and cyclohexene ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R¹ substituent and cyclohexene ring are attached to

35 substitutable carbon atoms 1,2- or 1,3- relative to each other,

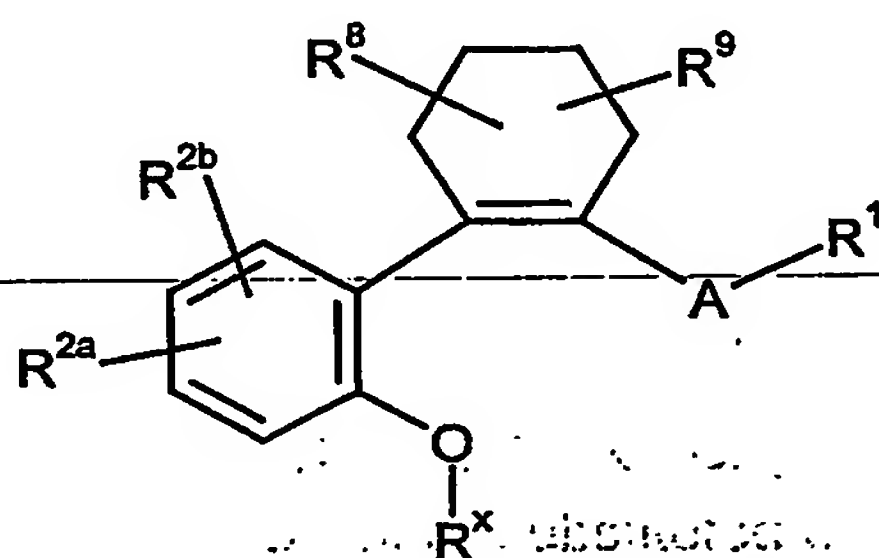
or a derivative thereof.

2. A compound according to claim 1 wherein A is selected from phenyl, pyridyl, pyridazinyl, pyrazinyl and pyrimidinyl, all of which may be optionally substituted.

3. A compound according to claim 1 or claim 2 wherein R^1 represents CO_2H .

4. A compound according to any one of claims 1 to 3 wherein A is a six membered ring and R^1 is attached to the group A in the 3 position relative to the bond attaching A to the cyclohexene ring.

5. A compound according to any one of claims 1 to 4 which is a compound of formula (IA):



(IA)

wherein:

A is an optionally substituted 5- or 6- membered heterocyclyl ring:

R^1 is CO_2R^4 ;

R^{2a} and R^{2b} are independently hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy and CN;

R^x is optionally substituted CO_2 -aryl;

R^4 is hydrogen or an optionally substituted alkyl;

when A is a 6-membered ring the R^1 substituent and cyclohexene ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and cyclohexene ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other or a derivative thereof

6. A compound selected from:

6-[2-(5-chloro-2-[(4-fluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid;

6-[2-(5-chloro-2-[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid;

6-[2-(5-Chloro-2-[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclohexen-1-yl]-2-pyridinecarboxylic acid;

or a derivative thereof.

5

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof together with a pharmaceutical carrier and/or excipient.

10

8. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for use as an active therapeutic substance.

15

9. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.

20

10. A method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE₂ at EP₁ receptors which comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

25

11. A method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

30

12. A method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

35

13. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.

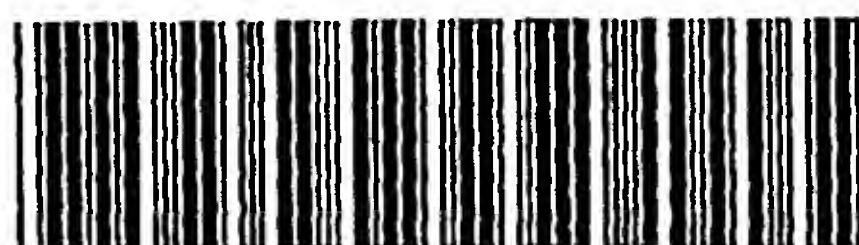
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14. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

15. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

5 16. A compound of formula (I) or a derivative thereof, according to claim 1, substantially as hereinbefore described with reference to any one of the Examples.

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